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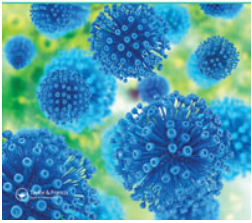
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Cerebral function parameters in people with HIV switching integrase inhibitors: a randomized controlled trial

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Background: Different antiretroviral therapies (ARTs) may have differing effects on central nervous system (CNS) function. We assessed CNS pharmacodynamic effects of switching integrase inhibitors in people-with-HIV (PWH).

Methods: PWH on tenofovir-DF/emtricitabine plus raltegravir 400mg twice daily with suppressed plasma HIV RNA and without overt neuropsychiatric symptoms were randomly allocated on a 1:2 basis to remain on raltegravir or switch to dolutegravir 50mg once daily for 120 days. Pharmacodynamic parameters assessed included cognitive function (z-score of 7 domains), patient-reported outcome measures (PROMs; PHQ-9 and Beck's depression questionnaires), cerebral metabolite ratios measured by proton magnetic resonance spectroscopy (¹H-MRS) and plasma and cerebrospinal fluid (CSF) HIV RNA. Pharmacokinetic parameters were also assessed in plasma and CSF. Changes and factors associated with changes in pharmacodynamics parameters were assessed.

Results: In 20 subjects (19 male, 14 white ethnicity, median age 43 years (IQR: 11.5) and CD4 + count 717 (SD: 298) cells/μL), over 120 days there were no statistically significant changes in cognitive function [mean z-score difference (95%CI) -0.004 (-0.38/0.37); *p* = 0.98], PROMs [PHQ-9 median score change: 0 in control arm, -0.5 switch arm (*p* = 0.57); Beck's depression questionnaire: -1.5 control arm, -1.0 switch arm (*p* = 0.38)], nor cerebral metabolite ratios between study arms. CSF HIV RNA was <5 copies/mL at baseline and day 120 in all subjects. Geometric mean pre-dose CSF dolutegravir concentration was 7.6 ng/mL (95% CI: 5.2–11.1).

Conclusions: Switching integrase inhibitor in virologically suppressed PWH without overt neuropsychiatric symptoms resulted in no significant changes in an extensive panel of CNS pharmacodynamics parameters.

KEYWORDS: Cognitive function, integrase inhibitor, raltegravir, dolutegravir, CNS, MR spectroscopy; CSF

Introduction

Modern effective antiretroviral therapy (ART) suppresses plasma viremia and allows restoration of immune system function in persons with HIV (PWH). Consequently, in ART treated PWH, AIDS defining illnesses are now rare and life expectancy approaches that of the general population.¹ However, when compared to the general population, the prevalence of non-

infectious co-morbidities are reported to be greater and quality of life is described to be poorer in PWH.²

Central nervous system (CNS) disorders are one group of conditions which remain highly prevalent in otherwise effectively treated PWH. This includes neuropsychiatric disorders such as depression, anxiety and cognitive impairment.^{3,4} Evidence suggests that different antiretroviral agents and combinations may have differing effects on cerebral function and neuropsychiatric symptomatology.^{5–7} The non-nucleoside-reverse-transcriptase-inhibitor efavirenz has well documented neuropsychiatric side effects⁸ and in more

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recent years, a host of CNS side effects (such as sleep disorders, dizziness, depression or anxiety) have been reportedly associated with the use of the HIV-integrase strand-transfer-inhibitors.^{9–13} These CNS side effects have been more frequently observed in certain populations, such as older patients, female individuals or in PWH with underlying depression or anxiety disorders.^{14,15}

Our aim here was to assess the pharmacodynamic effects on the CNS of two different integrase-inhibitor containing ART regimens. To assess this, we employed a comprehensive battery including cognitive assessments, patient reported outcome measures (PROMs), measurement of CNS metabolites using *in vivo* magnetic resonance spectroscopy (MRS) imaging and measurement of several cerebrospinal fluid parameters including HIV-1 RNA, soluble biomarkers and infectivity markers. Pharmacokinetic parameters were also assessed and included integrase-inhibitor drug exposure in plasma and cerebrospinal fluid.

Methods

Subject selection and study design

This prospective, randomized, single center, proof of concept study was conducted at St. Mary's Hospital (Imperial College Healthcare NHS Trust, London, UK) from July 2015 to August 2016. PWH on ART comprising of raltegravir 400 mg twice daily plus tenofovir/emtricitabine 245/200 mg (TruvadaTM) with an undetectable plasma HIV-1 RNA for at least 3 months with no neurological or cognitive complaints were eligible. Exclusion criteria included previous exposure to dolutegravir, significant neurological disease, current history of major depression or psychosis, recent head injury (prior 3 months) and current alcohol abuse or drug dependence.

Individuals were randomized on a 1:2 basis to either remain on raltegravir (*control arm*) or to switch integrase inhibitor from raltegravir to dolutegravir 50 mg once daily (*switch arm*). At baseline and after 120 days, all subjects underwent assessment of cerebral function parameters.

Ethical considerations

Local human ethics committee approval was granted prior to recruiting participants by the National Research Ethics Service Committee London-Central, UK (REC number 14/LO/1864). All participants were required to sign an informed consent before undergoing any screening procedures. The study was registered on the European Clinical Trials Database (EudraCT number 2014-003710-84).

Cerebral function parameters

Cognitive testing and patient reported outcome measures

Cognitive testing and PROMs were undertaken at baseline, day 60 and day 120. Cognitive testing comprised of a computerized battery (CogStateTM Ltd, Melbourne, Australia) which has been validated for cognitive testing in several disease areas including HIV.¹⁶ The battery undertaken in this study took approximately 30 min to complete and comprised of 7 specific tests covering several cognitive domains (attention, psychomotor function, visual and working memory and associate learning). PROMs were Lawton's instrumental activities of daily living scale,¹⁷ Patient Health Questionnaire-9 (PHQ-9)¹⁸ and Beck's depression questionnaires.¹⁹

Neuroimaging

Cerebral proton magnetic resonance spectroscopy (¹H-MRS) was performed on a Siemens MAGNETOMTM Verio 3 Tesla scanner (Siemens Healthcare GmbH, Erlangen, Germany) at baseline and day 120 with methods previously described in detail.²⁰

Post-processing of MRS were analyzed using the time-domain fitting algorithm Totally Automatic Robust Quantitation in NMR (TARQUINTM) (version 4.3.5).²¹ Metabolites identified included *N*-acetyl aspartate (NAA), Choline (Cho), myo-inositol (mI), and creatine (Cr) with all metabolites expressed as ratios to Cr.

Cerebrospinal fluid parameters

Cerebrospinal fluid examinations were undertaken at baseline and day 120 prior to administration of ART. Analyses included ultrasensitive HIV-1 RNA, anti-retroviral drug concentration (plasma concentration also measured), tryptophan/phenylalanine metabolites, neopterin, and infectivity assays.

Cerebrospinal fluid HIV-1 RNA was measured using a high sensitivity in-house assay with a detection limit of 5 RNA copies/mL.²² Concentrations of raltegravir and dolutegravir were analyzed by high-performance-liquid-chromatography (HPLC) tandem mass spectrometry.²³ The lower limits of quantification (LLQ) in plasma and cerebrospinal fluid were, respectively, 5 and 1.95 ng/mL for raltegravir alongside 10 and 0.75 ng/mL for dolutegravir.

Plasma and cerebrospinal fluid concentrations of tryptophan, kynurenine, phenylalanine, tyrosine and neopterin were measured using previously described methodologies.²⁴ The kynurenine/tryptophan and phenylalanine/tyrosine ratios were calculated as

indexes of indoleamine 2,3-dioxygenase (IDO-1) and phenylalanine hydroxylase (PAH) activity, respectively.

Cerebrospinal fluid infectivity assays were undertaken using cell cultures as previously described in detail.²⁵

Statistical analysis

All statistical analyses were performed using SPSS (version 24.0; SPSS Inc., Chicago, IL, USA). As a proof of concept study, no specific power calculations were undertaken.

Cognitive results were analyzed in accordance with CogState™ recommendations. Z-standardized scores for each participant in each cognitive task were estimated using task-specific means and standard deviations at baseline. Data are presented as global cognitive scores, calculated as a composite of all cognitive tasks. Where necessary, change of sign was undertaken in order for the scoring of all tasks to be unidirectional (the higher the score, the better the performance).

Means and standard deviation of cerebral metabolite ratios were calculated. Absolute changes in cerebral metabolite ratios between baseline and follow-up were evaluated using a paired sample *t*-test.

Geometric means (GM) and 95% confidence intervals (CIs) were calculated for cerebrospinal fluid and plasma concentrations of raltegravir and dolutegravir. The CIs were first determined using logarithms of the individual GM values and then the calculated values were expressed as linear values. A coefficient of variation (CV, [(standard deviation/mean) × 100]) was used to express inter-patient variability in the pharmacokinetic parameters.

Comparisons between the study arms for cerebral function parameters were undertaken using appropriate statistical methods which included paired and independent *t*-tests, chi-squared or Fisher's exact tests and Mann-Whitney *U*-test. Spearman's rank correlation was used to investigate associations between changes in PROMs and cerebral metabolite ratios.

For the tryptophan pathway metabolites, paired-samples *t*-tests were undertaken to assess changes in plasma and cerebrospinal fluid concentrations over the study period for each arm independently. Pearson *r* correlations were used to determine associations between cerebral parameters and global cognitive scores for all subjects at baseline. Mixed models were constructed to investigate the relationship between changes in metabolite concentrations in plasma and cerebrospinal fluid with the global cognitive score for subjects in the dolutegravir arm (*switch arm*) only. The

models fixed effects were global cognitive score (dependent variable) with the biomarker concentrations the independent variable. The alpha value was set at 0.05 for each analysis performed and not corrected for multiplicity.

Results

Subject characteristics

Of 28 participants screened, 22 were randomized and 20 completed study procedures (8 in the *control arm* and 12 in the *switch arm*, see Figure 1). Baseline characteristics are shown in Table 1. Study drugs were generally well-tolerated with all patients reporting over 95% adherence to therapy. No safety or laboratory concerns related to study drugs were observed. One patient in the *switch arm* died during the study follow-up due to complications arising from a previously undiagnosed metastatic malignancy. At day 120, plasma HIV-1 RNA was <20 copies/mL in all subjects.

Cognitive results and patient reported outcome measures

Baseline cognitive performance and changes over the study period as shown in Table 2. No statistically significant differences between the study groups were observed in changes in global cognitive score or in individual cognitive domains (all *p*-values >0.1). No differences in changes in depression questionnaires between the study arms were observed at day 120 from baseline (*p* = 0.57 for PHQ-9 and *p* = 0.38 for Beck's, see Table 2). The result of the Lawton's instrumental activities of daily living scale questionnaire was 8 for all patients at all time-points.

Neuroimaging

Cerebral metabolite ratio results are shown in Table 3. No statistically significant changes in cerebral metabolite ratio were observed over the study period between the two study treatment groups and no significant associations were observed between the PROMs and changes in cerebral metabolite ratios (*p* > 0.2 for all associations).

Cerebrospinal fluid and plasma parameters

In all individuals, cerebrospinal fluid HIV-1 RNA was undetectable (<5 copies/mL) at both baseline and day 120. Cerebrospinal fluid GM concentrations of raltegravir for the *control arm* at baseline (*n* = 8), *control arm* at day 120 (*n* = 8) and *switch arm* at baseline (*n* = 12) were 16.2 ng/mL (95% CI: 9.4–27.9), 15.0 ng/mL (95% CI: 8.6–26.3) and 14.8 ng/mL (95% CI: 8.2–26.8), respectively. Cerebrospinal fluid GM

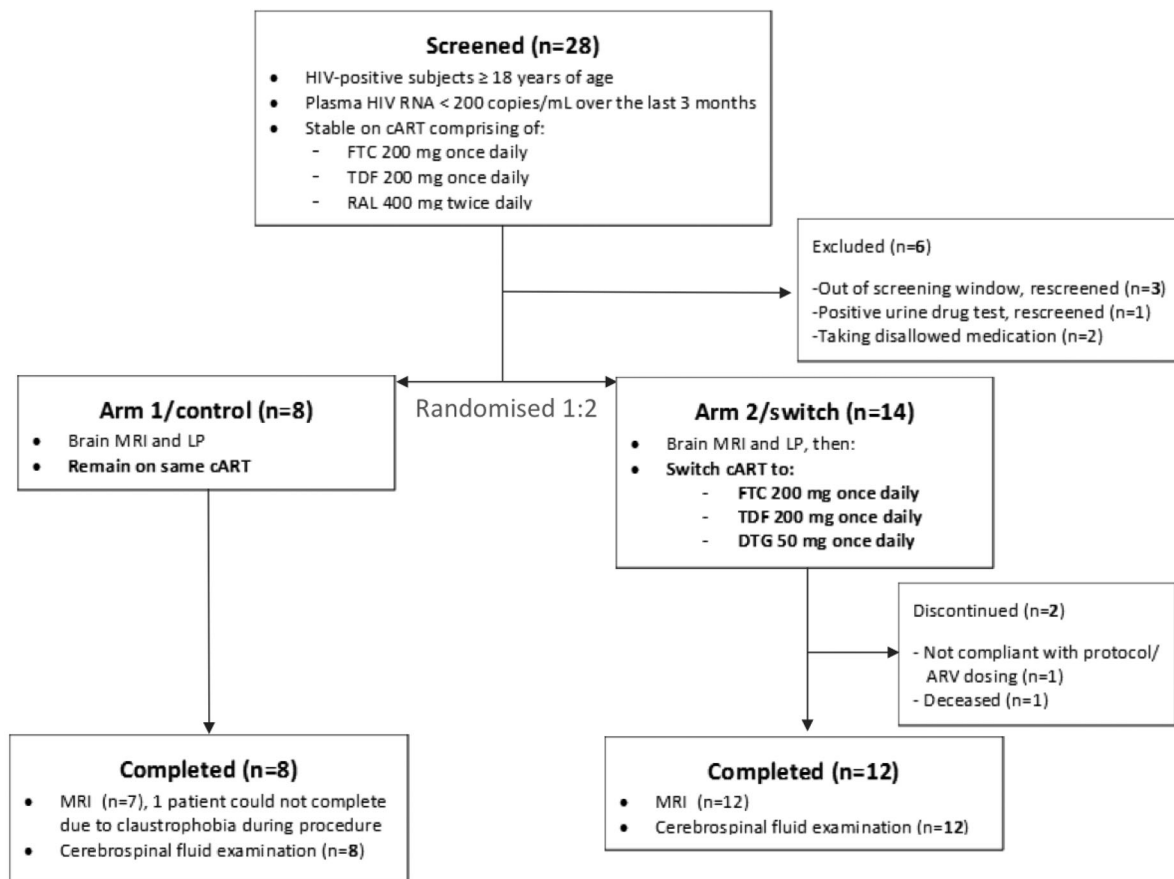


Figure 1 legend: FTC=emtricitabine; TDF=tenofovir disoproxil fumarate, RAL= raltegravir;

DTG=Dolutegravir; MRI=magnetic resonance imaging; LP=lumbar puncture; ARV=antiretroviral.

Figure 1. Consort diagram of participant flow. ARV, antiretroviral; DTG, dolutegravir; FTC, emtricitabine; LP, lumbar puncture; MRI, magnetic resonance imaging; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Table 1. Participant demographics and clinical characteristics.

		Study arms	
Parameter	Overall	Control arm	Switch arm
<i>Mean (SD) unless otherwise stated</i>			
N	21	8	13
Age, years (IQR)	43 (11.5)	39.5 (15.5)	43 (13)
Male, n (%)	20 (95.2)	7 (87.5)	13 (100)
Ethnicity (%)			
White	14 (66.7)	5 (62.5)	9 (69.2)
Black	2 (9.5)	1 (12.5)	1 (7.7)
Other	5 (23.8)	2 (25)	3 (23)
BMI	26.1 (3.2)	27.4 (3.4)	25.4 (2.9)
Baseline absolute CD4+ count (cells/μL)	717 (298)	688 (395)	736 (237)
Baseline CD4+ percentage, median (IQR)	34 (14.5)	35.5 (24.2)	34 (13)
<i>Day 120 parameters</i>			
Number completing all study procedures	20	8	12
HIV RNA <20 copies/mL, n (%)	20 (100)	8 (100)	12 (100)
Absolute CD4+ count (cells/uL)	768 (389)	807 (535)	742 (277)

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

concentrations of dolutegravir for the *switch arm* at day 120 ($n = 12$) was 7.6 ng/mL (95% CI: 5.2–11.1). See Table 4 for full pharmacokinetic results.

Concentrations of tryptophan, kynurenine, phenylalanine, tyrosine, and neopterin, and the tryptophan/kynurenine and phenylalanine/tyrosine ratios, are

Table 2. Changes in cognitive function and patient reported outcome measures by study arm at day 120.

	Baseline		Changes at day 120 from baseline			
	Control arm	Switch arm	Control arm	Switch arm	Difference control vs. switch arm	
	N = 8	N = 12	N = 8	N = 12	Mean score difference (95%CI)	p-value
<i>Cognitive testing, Z-score^a (SD)</i>						
Global cognitive score	0.25 (0.54)	−0.15 (0.70)	0.14 (0.37)	0.14 (0.40)	−0.004 (−0.38/0.37)	0.98
<i>Patient reported outcome measures, median (range)</i>						
Patient Health Questionnaire-9	2 (0/6)	2 (0/9)	0 (−5/1)	−0.5 (−5/3)	–	0.57 ^b
Beck's depression questionnaire	3 (1/12)	1 (0/20)	−1.5 (−10/2)	−1.0 (−15/9)	–	0.38 ^b

CI, confidence interval; SD, standard deviation.

^aLower result represents worse performance; higher results represent better performance.^bIndependent samples Mann–Whitney U-test.**Table 3. Changes in cerebral metabolites over 120 days and correlations with depression questionnaires.**

Cerebral metabolite ratios	Baseline values, mean (SD)		Change between study groups over 120 days, mean (SD)			Correlation with change in depression questionnaires	
	Control arm	Switch arm	Control arm	Switch arm	Control vs. switch arm	Correlation coefficient (p-value)	
	n = 8	n = 12	n = 7	n = 12	p-value	PHQ-9 ^a	Beck's ^a
<i>Frontal gray matter</i>							
NAA/Cr	1.04 (0.11)	1.00 (0.09)	−0.06 (0.16)	0.08 (0.14)	0.07	−0.38 (0.10)	−0.22 (0.36)
Cho/Cr	0.22 (0.02)	0.24 (0.03)	0.01 (0.02)	−0.01 (0.04)	0.21	0.43 (0.06)	0.36 (0.13)
ml/Cr	0.57 (0.06)	0.58 (0.11)	0.04 (0.03)	0.07 (0.41)	0.85	0.13 (0.60)	−0.27 (0.25)
<i>Frontal white matter</i>							
NAA/Cr	1.28 (0.41)	1.16 (0.15)	−0.13 (0.34)	0.01 (0.13)	0.20	−0.18 (0.44)	0.08 (0.73)
Cho/Cr	0.32 (0.04)	0.31 (0.04)	0.004 (0.05)	0.01 (0.05)	0.75	−0.26 (0.28)	−0.07 (0.78)
ml/Cr	0.71 (0.19)	0.63 (0.12)	0.02 (0.05)	0.005 (0.11)	0.82	0.09 (0.72)	−0.01 (0.95)
<i>Right basal ganglia</i>							
NAA/Cr	0.97 (0.18)	0.92 (0.20)	−0.13 (0.24)	0.0066 (0.33)	0.35	−0.06 (0.80)	0.006 (0.98)
Cho/Cr	0.25 (0.02)	0.23 (0.02)	−0.03 (0.03)	−0.004 (0.05)	0.21	−0.03 (0.89)	0.14 (0.56)
ml/Cr	0.48 (0.10)	0.38 (0.10)	−0.04 (0.10)	0.07 (0.19)	0.16	0.10 (0.65)	0.23 (0.33)

Cho, choline; Cr, creatinine; ml, myoinositol; NAA, N-acetyl aspartate; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation.

^aCorrelation between change in cerebral metabolite ratios over 120 days and change in questionnaires over 120 days.**Table 4. Pharmacokinetic parameters of integrase inhibitors in plasma and cerebrospinal fluid over the study period.**

Antiretroviral concentration (ng/mL)	Overall N = 20		Control arm N = 8		Switch arm N = 12	
	GM (95%CI)	CV%	GM (95%CI)	CV%	GM (95%CI)	CV%
<i>Raltegravir at baseline</i>						
Plasma	116 (66–204)	93.8	102 (34–310)	109.9	126 (59–266)	87.6
CSF ^a	15.4 (10.5–22.4)	66.3	16.2 (9.4–27.9)	60.6	14.8 (8.2–26.8)	72.0
CSF:plasma %	13.0 (8.6–19.4)	122.9	15.8 (6.4–39.3)	125.7	11.2 (7.4–17.0)	51.7
<i>Raltegravir at follow-up</i>						
Plasma	–	–	107 (39–293)	113.6	–	–
CSF	–	–	15.0 (8.6–26.3)	73.5	–	–
CSF:plasma %	–	–	14.0 (7.3–26.9)	74.7	–	–
<i>Dolutegravir at follow-up</i>						
Plasma	–	–	–	–	1052 (742–1492)	58.3
CSF	–	–	–	–	7.6 (5.2–11.1)	54.7
CSF:plasma %	–	–	–	–	0.7 (0.6–0.8)	28.4

CSF, cerebrospinal fluid; CV, coefficient of variation; GM, geometric mean.

^aOne patient with [raltegravir]_{CSF} < LLQ (1.950 ng/mL) in switch group.

shown in Table 5. In the *switch arm*, mean plasma concentration of tryptophan increased significantly from baseline to day 120 (mean increase, 4.84 µmol/L;

$p = 0.038$; 95% CI, 0.32–9.37). No other statistically significant changes in concentrations of the other measured plasma biomarkers were observed in either

Table 5. Tryptophan metabolism parameters in plasma and CSF over study period.

Parameter	Baseline result		Changes at 120 days		Control vs. Switch arm <i>p</i> -value*
	Control arm (RAL) <i>n</i> = 8	Switch arm (DTG) <i>n</i> = 12	Control arm (RAL) <i>n</i> = 8	Switch arm (DTG) <i>n</i> = 12	
<i>Plasma</i>					
TRP; μmol/L, mean (SD)	51.15 (10.56)	50.15 (8.03)	−4.06 (6.61)	4.84 (7.12)	0.011
KYN; μmol/L, mean (SD)	1.98 (0.78)	2.07 (0.69)	−0.06 (0.40)	0.10 (0.64)	0.541
KYN/TRP ratio; μmol/mmol, mean (SD)	38.82 (12.90)	41.15 (9.49)	3.24 (11.63)	−0.55 (12.60)	0.506
PHE; μmol/L, mean (SD)	61.65 (7.55)	58.38 (9.05)	−3.83 (11.36)	3.82 (8.90)	0.109
TYR; μmol/L, mean (SD)	65.34 (8.49)	65.44 (15.00)	−1.38 (14.82)	3.78 (10.76)	0.378
PHE/TYR ratio; μmol/mmol, mean (SD)	0.96 (0.15)	0.92 (0.18)	−0.03 (0.17)	0.01 (0.14)	0.589
NEO; nmol/L, mean (SD)	11.83 (8.50)	12.30 (5.89)	3.61 (11.55)	5.23 (15.42)	0.803
<i>Cerebrospinal fluid</i>					
TRP; μmol/L, mean (SD)	1.58 (0.68)	1.67 (0.26)	0.02 (0.33)	0.17 (0.43)	0.406
KYN; μmol/L, mean (SD)	0.07 (0.03)	0.06 (0.03)	−0.01 ^a (0.01)	0.01 ^b (0.01)	0.130
KYN/TRP ratio; μmol/mmol, mean (SD)	43.39 (29.17)	38.77 (15.78)	−5.27 ^a (10.95)	−0.48 ^b (10.79)	0.513
PHE; μmol/L, mean (SD)	12.31 (2.43)	11.73 (2.02)	−0.33 (1.60)	0.22 (2.17)	0.553
TYR; μmol/L, mean (SD)	12.38 (3.28)	11.83 (2.61)	−0.14 (2.81)	0.82 (1.94)	0.379
PHE/TYR ratio; μmol/mmol, mean (SD)	1.01 (0.10)	1.01 (0.16)	0.00 (0.18)	−0.04 (0.14)	0.565
NEO; nmol/L, mean (SD)	9.19 (8.20)	7.70 (4.26)	−1.93 (2.54)	0.23 (2.03)	0.049

CI, confidence interval; DTG, dolutegravir; KYN, kynurenine; NEO, neopterin; PHE, phenylalanine; RAL, raltegravir; SD, standard deviation; TRP, tryptophan; TYR, tyrosine.

^a *n* = 4.

^b *n* = 6.

*Unadjusted *p*-value.

arm. Statistically significant differences in plasma tryptophan ($p = 0.011$) and cerebrospinal fluid neopterin concentrations ($p = 0.049$) were observed between arms at day 120.

All cerebrospinal fluid samples displayed dose–response curves allowing quantification of antiretroviral activity on infectivity assays. At a 1:4 dilution, all cerebrospinal fluid samples from both study arms presented near-maximal inhibition at both time points. Infectivity model half maximal inhibitory IMIC_{50} expressed as CNS Anti-Retroviral scores ($-\text{Log}_2\text{IMIC}_{50}$) of cerebrospinal fluid samples did not show statistically significant changes between baseline and day 120 for both study groups ($p = 0.36$ for control group and $p = 0.27$ for switch group).

Associations with tryptophan metabolites

No statistically significant associations were observed between plasma kynurenine or tyrosine pathway metabolites and global cognitive scores at baseline (all p values > 0.1). Cerebrospinal fluid phenylalanine concentrations positively correlated with baseline global cognitive scores ($r = 0.49$, unadjusted $p = 0.024$), as did cerebrospinal fluid phenylalanine/tyrosine ratios ($r = 0.57$, unadjusted $p = 0.007$).

In the mixed model analysis of the *switch arm* (dolutegravir), plasma kynurenine/tryptophan ratio concentrations correlated with changes in global cognitive scores, such that for every $1 \mu\text{mol/L}$ increase

observed in kynurenine/tryptophan ratio, a 0.019-point decrease was observed in the global cognitive scores (unadjusted $p = 0.021$), indicating poorer cognitive performance as the kynurenine/tryptophan ratio increases. No other statistically significant associations were observed for the other biomarkers tested in either plasma or cerebrospinal fluid.

Discussion

In this randomized, prospective, proof of concept study, comparing switching integrase inhibitor-based ART in PWH without overt neuropsychiatric symptoms, we observed no differences in cognitive function or other cerebral function parameters over a 120-day period. Strengths of our study include the randomized approach to the study design and the detailed cerebral function assessments which were included, namely cognitive function, PROMs, neuroimaging parameters and several cerebrospinal fluid parameters.

In large cohort studies, neuropsychiatric adverse events have been frequently observed in PWH on integrase inhibitors, with the presence of these neuropsychiatric adverse events associated with an increased risk of discontinuing ART therapies.¹³ We specifically recruited PWH without overt neurological symptomatology. During the follow up period no neuropsychiatric adverse events evolved in our study. It is likely the population we have recruited were less prone to develop such neuropsychiatric side effects given we

recruited individuals tolerating a raltegravir containing ART regimen without adverse events and who were willing to switch the integrase inhibitor component of their ART regimen.²⁶

In a retrospective cross-sectional study assessing tryptophan metabolism in individuals with acute HIV infection, increased kynurenine/tryptophan ratios are described to be associated with increased depressive symptoms.²⁷ Furthermore, in PWH with cognitive impairment higher phenylalanine/tyrosine ratios, representing an increased CNS PAH activity, were observed when compared to PWH without cognitive disorders.²⁷ In another retrospective cross-sectional study in virologically suppressed PWH, higher phenylalanine/tyrosine ratios were observed, but these were not associated with cognitive impairment.²⁴ Also, a trend towards lower plasma kynurenine/tryptophan ratios was associated with both cognitive impairment and depression.²⁴ In a further prospective study assessing PWH switching from efavirenz-based ART to dolutegravir-based ART, an increase in plasma kynurenine concentrations and improvements in CNS toxicity scores was reported.²⁸ In our study, we did not observe differences in either phenylalanine/tyrosine ratio in plasma or cerebrospinal fluid between study arms. However, plasma kynurenine/tryptophan ratios were found to be negatively correlated with lower global cognitive scores in the switch arm. These results should be interpreted with caution since this model was not adjusted for multiplicity and changes in the kynurenine/tryptophan ratio or global cognitive score were not observed separately in the individual study arms. In addition, this significant relationship was not present for the cerebrospinal fluid kynurenine/tryptophan ratio.

A difference in mean plasma tryptophan concentrations was observed between the study groups ($p = 0.011$) at day 120. This appears to be driven by an increase in plasma tryptophan in the switch arm (mean change $4.84 \mu\text{mol/L}$; SD: 7.12) and a decrease in the control arm (mean change $-4.6 \mu\text{mol/L}$; SD: 6.61). Corresponding changes in kynurenine concentrations or the kynurenine/tryptophan ratio were not observed indicating that the observed changes are unlikely related to changes in IDO-1 enzyme activity as both changes in tryptophan and kynurenine concentrations would be expected. Given these differences are unlikely to be related to changes in IDO-1 enzyme activity it is possible the differences are not related to ART treatment effects in our study. Other possible explanations for the changes in plasma tryptophan concentration we have observed may be related to dietary intake which is known to affect plasma tryptophan

concentration.^{29,30} We did not undertake dietary assessments in our study to assess any changes in dietary intake. Another limitation of the study is the lack of a negative HIV control group. This prevents from examining the associations of cerebral function parameters and tryptophan/phenylalanine metabolites.

We observed a difference in mean cerebrospinal fluid neopterin concentration between study arms at follow up ($p = 0.049$). This change in cerebrospinal fluid neopterin concentration was not associated with any other clinical parameters and therefore any clinical relevance of this observation is unclear. Neopterin was included as a marker of immune activation based on its correlation with IDO activity.³¹

In a proof of concept study like this, the use of indicators of effect size could be very relevant to establish a hypothesis where non-statistically significant results are observed. This is the case for a trend of NAA/Cr ratio changes in the frontal gray matter favoring the switch arm ($p = 0.07$). However, this finding in isolation is particularly difficult to interpret since that difference involves an unexplained and unexpected worsening in NAA/Cr ratio in the control arm. See Table 3.

Cerebrospinal fluid concentrations of dolutegravir [7.6 ng/mL (95% CI, $5.2\text{--}11.1$)] were in a similar range to those previously reported [13 ng/mL (range, $4\text{--}18 \text{ ng/mL}$)].³² Other studies have described associations between dolutegravir cerebrospinal fluid concentration and neuropsychiatric adverse events.³³ Given our study comprised of PWH without overt neuropsychiatric adverse events, we do not have the ability to link the cerebrospinal fluid exposure of dolutegravir to such events. Other limitations of our study are the small sample size, the relative young age of the participants and the small number of female participants.¹⁴

In summary, we observed no significant changes in clinical, cerebral imaging parameters or cerebrospinal fluid biomarkers in this comprehensive assessment of cerebral pharmacodynamic and pharmacokinetic parameters in virologically suppressed PWH without overt neuropsychiatric switching integrase inhibitor.

Disclosure statement

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